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=> s decitabine
L1          279 DECITABINE

=> s cancer or tumor or antitumor or anticancer or antineoplastic or malignant
   4 FILES SEARCHED...
L2      4193477 CANCER OR TUMOR OR ANTITUMOR OR ANTICANCER OR ANTINEOPLASTIC OR
                MALIGNANT

=> s l1 (p) l2
L3          121 L1 (P) L2

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FIELD CODE - 'AND' OPERATOR ASSUMED 'L33 (P) TREAT?'
L5           23 L4 (P) TREAT?

=> d l5 1-23 ibib abs

L5   ANSWER 1 OF 23     MEDLINE
ACCESSION NUMBER:   2002254399     IN-PROCESS
DOCUMENT NUMBER:    21989084   PubMed ID: 11993784
TITLE:              Current therapy of chronic myelogenous leukemia.
AUTHOR:             Garcia-Manero Guillermo; Talpaz Moshe; Kantarjian Hagop M
CORPORATE SOURCE:   Department of Leukemia and Bioimmunotherapy, University of
                    Texas M.D. Anderson Cancer Center, Houston 77030, USA.
SOURCE:             INTERNAL MEDICINE, (2002 Apr) 41 (4) 254-64.
                    Journal code: 9204241. ISSN: 0918-2918.
PUB. COUNTRY:       Japan
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20020508
                    Last Updated on STN: 20020508
AB   Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder
     molecularly defined by the BCR-ABL gene and its products. The protein
     encoded by this chimeric gene is a constitutively activated tyrosine
     kinase that alters multiple signal transduction pathways inducing
       ***malignant***   transformation. Until recently,   ***treatment***
     options for patients with CML consisted of hydroxyurea, interferon-based
     therapies or allogeneic stem cell transplantation (alloSCT).
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Treatment decisions were generally based on the age of the patient and the phase of the disease. Recently, several new therapies have been developed that may change the natural history of CML and patient prognosis. In particular imatinib mesylate (ST1571, Gleevec) an oral Bcr-Abl kinase inhibitor, has demonstrated activity in all phases of CML, and may replace interferon and alloSCT as the initial therapy for this disease. Other agents and therapies with potential value, either alone or in combination, include polyethyleneglycol (PEG) interferon, homoharringtonine, ***decitabine*** , oral cytarabine, and growth factor modulation. In this article, we discuss the biological and clinical characteristics of CML, as well as the different therapeutic alternatives for patients with this disorder.

L5 ANSWER 2 OF 23 MEDLINE
ACCESSION NUMBER: 2002135976 MEDLINE
DOCUMENT NUMBER: 21674725 PubMed ID: 11815248
TITLE: Somatic recombination: a major genotoxic effect of two pyrimidine antimetabolitic chemotherapeutic drugs in Drosophila melanogaster.
AUTHOR: Cunha Kenya Silva; Reguly Maria Luiza; Graf Ulrich; de Andrade Heloisa Helena Rodrigues
CORPORATE SOURCE: Departamento de Ciencias Fisiologicas, Universidade Federal de Goias, CP 131, 74001-970, GO, Goiania, Brazil.
SOURCE: MUTATION RESEARCH, (2002 Feb 15) 514 (1-2) 95-103.
Journal code: 0400763. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020302
Last Updated on STN: 20020403
Entered Medline: 20020328
AB Two deoxycytidine analogues, 1-beta-D-arabinofuranosylcytosine (cytosine arabinoside, citarabine, araC) and 5-aza-2'-deoxycytidine (***decitabine*** , DAC, 5-aza-dC), are the drugs of choice in the ***treatment*** of acute myeloid leukaemia. The araC-induced cytotoxicity is a direct result of its interference with nucleic acids synthesis, whereas 5-aza-dC is a potent suppressor of DNA methylation. We employed the standard version of the wing somatic mutation and recombination test (SMART) in Drosophila melanogaster to evaluate the genotoxic potential of these two antimetabolites as a function of exposure concentration. In addition, we determined the relative contributions of mutational and recombinational events to total genotoxicity. The compounds were administered by chronic feeding of 3-day-old larvae. Our results indicate that recombinagenicity is the major genotoxic effect of araC and 5-aza-dC (approximately, 77 and 81%, respectively, recombination). The standardised clone induction frequencies (per mM concentration per cell per cell division) show that 5-aza-dC is 85 times more powerful then araC (inducing approximately 58 mutant clones per 10(5) cells per mM). The high recombinagenic activity of these two drugs suggests that--despite their therapeutic effects against ***cancer*** --a question is raised whether these drugs should be considered for adverse effects in ***cancer*** chemotherapy.

L5 ANSWER 3 OF 23 MEDLINE
ACCESSION NUMBER: 2001648094 MEDLINE
DOCUMENT NUMBER: 21557245 PubMed ID: 11700387
TITLE: Targeting hypomethylation of DNA to achieve cellular differentiation in myelodysplastic syndromes (MDS).
AUTHOR: Silverman L R
CORPORATE SOURCE: Division of Medical Oncology, Mount Sinai School of Medicine, New York, New York 10029, USA..
lewis.silverman@mssm.edu
SOURCE: ONCOLOGIST, (2001) 6 Suppl 5 8-14. Ref: 40
Journal code: 9607837. ISSN: 1083-7159.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 11112
Last Updated on STN: 20020124
Entered Medline: 20011231

AB Considerable progress has been made recently in defining and understanding the diverse members of the group of hematologic disorders now known as the myelodysplastic syndrome (MDS). New systems of classification, based on the latest cytogenetic methodologies, have generated better prognostic data, and basic research has more closely associated molecular mechanisms with clinical subgroups. The mechanisms underlying most cases of myelodysplasia appear to be an array of chromosomal abnormalities leading to suppression of normal myeloid cell differentiation and dominance of abnormal, immature cells. The process is progressive and is mediated by a variety of cytokines, potential loss of ***tumor*** suppressor genes, aberrations in signal transduction pathways, and perhaps immune mechanisms. Hypermethylation of specific DNA sequences has been implicated in the pathogenesis of MDS. Until recently, ***treatment*** options have been few, high risk, and mostly ineffective. New discoveries, particularly in the area of stimulating remaining normal myeloid cells to resume growth and differentiation, hold promise for safer ***treatment*** regimens and improved outcomes. Among the promising new agents are nucleoside analogues, such as 5-azacytidine and ***decitabine*** , which reactivate ***tumor*** suppressor gene transcription through effects on DNA methylation.

L5 ANSWER 4 OF 23 MEDLINE
ACCESSION NUMBER: 2001161950 MEDLINE
DOCUMENT NUMBER: 21160236 PubMed ID: 11259619
TITLE: Activation of the p53 DNA damage response pathway after inhibition of DNA methyltransferase by 5-aza-2'-deoxycytidine.
AUTHOR: Karpf A R; Moore B C; Ririe T O; Jones D A
CORPORATE SOURCE: Division of Molecular Pharmacology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah 84112, USA.
SOURCE: MOLECULAR PHARMACOLOGY, (2001 Apr) 59 (4) 751-7.
Journal code: NGR; 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB Transcriptional silencing of ***tumor*** suppressor genes by DNA methylation occurs in ***cancer*** cell lines and in human ***tumors*** . This has led to the pursuit of DNA methyltransferase inhibition as a drug target. 5-Aza-2'-deoxycytidine [5-aza-CdR (***decitabine***)], a potent inhibitor of DNA methyltransferase, is a drug currently in clinical trials for the ***treatment*** of solid ***tumors*** and leukemia. The efficacy of 5-aza-CdR may be related to the induction of methylation-silenced ***tumor*** suppressor genes, genomic hypomethylation, and/or enzyme-DNA adduct formation. Here, we test the hypothesis that 5-aza-CdR ***treatment*** is perceived as DNA damage, as assessed by the activation of the ***tumor*** suppressor p53. We show that 1) colon ***tumor*** cell lines expressing wild-type p53 are more sensitive to 5-aza-CdR mediated growth arrest and cytotoxicity; 2) the response to 5-aza-CdR ***treatment*** includes the induction and activation of wild-type but not mutant p53 protein; and 3) the induction of the downstream p53 target gene p21 is partially p53-dependent. The induction of p53 protein after 5-aza-CdR ***treatment*** did not correlate with an increase in p53 transcripts, indicating that hypomethylation at the p53 promoter does not account for the p53 response. It is relevant that 5-aza-CdR has shown the greatest promise in clinical trials for the ***treatment*** of chronic myelogenous leukemia, a malignancy in which functional p53 is often retained. Our data raise the hypothesis that p53 activation may contribute to the clinical efficacy and/or toxicity of 5-aza-CdR.

L5 ANSWER 5 OF 23 MEDLINE
ACCESSION NUMBER: 2001064568 MEDLINE

DOCUMENT NUMBER: 20551236 PubMed ID: 11098088
TITLE: 5-Aza-2'-deoxycytidine leads to down-regulation of aberrant p16INK4A RNA transcripts and restores the functional retinoblastoma protein pathway in hepatocellular carcinoma cell lines.
AUTHOR: Suh S I; Pyun H Y; Cho J W; Baek W K; Park J B; Kwon T; Park J W; Suh M H; Carson D A
CORPORATE SOURCE: Department of Microbiology and Institute for Medical Science, School of Medicine, Keimyung University, 194 Dong San Dong Jung-Gu, 700-712, Taegu, South Korea.. seong@dsmc.or.kr
SOURCE: CANCER LETTERS, (2000 Nov 10) 160 (1) 81-8.
Journal code: CMX. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222

AB The inactivation of the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor p16INK4A may be caused by gene deletion, mutation or promoter hypermethylation. We have previously reported that p16INK4A in hepatocellular carcinoma (HCC) tissues and cell lines is inactivated predominantly by promoter hypermethylation rather than genomic aberrations. In the present experiments, we have studied the effects of the demethylating agent, 5-aza-2'-deoxycytidine (5-AZA/ ***decitabine***), on the expression of aberrant p16INK4A RNA transcripts and the CDK-retinoblastoma gene pathway in HCC cell lines with p16INK4A promoter hypermethylation. The expression of aberrant p16INK4A RNA transcripts was down-regulated and p16INK4A protein was strongly re-expressed in the HCC cell lines, SNU 354, 398, 423 and 475 after 5-AZA/ ***decitabine*** ***treatment*** for 5 days. The re-expressed p16INK4A was functional, because it bound to and inhibited CDK4 kinase activity, and increased the concentrations of the hypophosphorylated form of retinoblastoma protein (pRB) in cells with a wild type RB gene. Moreover, ***treatment*** with the demethylating agent led not only to G1 cell cycle arrest, but also to the increased expression of the senescence-associated marker beta-galactosidase. This up-regulation of p16INK4A mRNA and protein correlated with demethylation of the p16INK4A promoter, and with the down-regulation or disappearance of aberrant p16INK4A transcripts. These results suggest that the aberrant p16INK4A RNA transcript can be transcribed from the methylated p16INK4A gene, and endogenous reactivation of functional p16INK4A mRNA by a demethylating agent can restore the pRB pathway in HCC, and foster the terminal differentiation of the ***malignant*** cells. Therefore, demethylating agents, such as 5-AZA/ ***decitabine*** , may have potential in the ***treatment*** of HCC.

L5 ANSWER 6 OF 23 MEDLINE
ACCESSION NUMBER: 2000420723 MEDLINE
DOCUMENT NUMBER: 20288954 PubMed ID: 10830142
TITLE: A phase I trial of cisplatin plus decitabine, a new DNA-hypomethylating agent, in patients with advanced solid tumors and a follow-up early phase II evaluation in patients with inoperable non-small cell lung cancer.
AUTHOR: Schwartsmann G; Schunemann H; Gorini C N; Filho A F; Garbino C; Sabini G; Muse I; DiLeone L; Mans D R
CORPORATE SOURCE: South-American Office for Anticancer Drug Development, and Hospital de Clinicas de Porto Alegre (HCPA-UFRGS), RS, Brazil.
SOURCE: INVESTIGATIONAL NEW DRUGS, (2000 Feb) 18 (1) 83-91.
Journal code: GWJ; 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915

Last Updated on STN: 20000915
Entered Medli[redacted] 20000901

AB The authors describe a phase I trial of cisplatin plus ***decitabine*** , a novel DNA-hypomethylating agent, in patients with advanced solid ***tumors*** , which was followed by an early phase II evaluation of the combination in patients with inoperable non-small cell lung ***cancer*** (NSCLC). In the phase I trial, cisplatin was studied at a fixed dose of 33 mg/m2, while ***decitabine*** was escalated in four (I-IV) dose escalation levels (45, 67, 90 to 120 mg/m2, respectively) in consecutive groups of at least 3 patients per dose level. Decytabine was administered to the patients as a two-hour intravenous infusion, while cisplatin was given intravenously immediately after the end of ***decitabine*** infusion. Both agents were given on days 1-3 every 21 days. Twenty-one patients were included in the phase I trial. Dose level IV (120 mg/m2 ***decitabine***) was considered the maximum tolerated dose (MTD), while the dose-limiting toxicities were neutropenia, thrombocytopenia and mucositis. The recommended doses for phase II trials in good- and poor-risk patients were 90 (level III) and 67 mg/m2 (level II), respectively. One short-lasting partial response was observed in a patient with cervical ***cancer*** , while two minor regression were documented in a patients with NSCLC and cervical ***cancer*** , respectively. Dose level II was selected for the phase II trial in patients with inoperable NSCLC. Fourteen consecutive patients were included in this part of the study. The median age of the patients was 57 years (range, 39-75), male/female ratio of 11/3 and a median WHO performance status 1 (0-2). The stage of disease were IIIB (5) and IV (9). Prior irradiation to the chest was given in one case. A total of 30 ***treatment*** courses were evaluable for toxicity and response, with a median of 2 courses per patient (1-4). Grade 3-4 neutropenia and thrombocytopenia were observed in about half of the cases. Mucositis, diarrhea, nausea and vomiting, and skin rash were also observed in some patients. Three minor responses were documented, which lasted for 4, 16 and 36 weeks. Median survival of patients was 15 weeks (4-38). In conclusion, the cisplatin plus ***decitabine*** combination did not exhibit significant ***antitumor*** activity in patients with NSCLC at the dose and schedule applied in this trial to justify its further evaluation in this patient population.

L5 ANSWER 7 OF 23 MEDLINE
ACCESSION NUMBER: 1999163424 MEDLINE
DOCUMENT NUMBER: 99163424 PubMed ID: 10068280
TITLE: Chronic myelogenous leukemia--progress at the M. D. Anderson Cancer Center over the past two decades and future directions: first Emil J Freireich Award Lecture.
AUTHOR: Kantarjian H M; Talpaz M; O'Brien S; Kurzrock R; Gutterman J; Keating M J; McCredie K B; Freireich E J
CORPORATE SOURCE: Department of Leukemia, M.D. Anderson Cancer Center, Houston, Texas 77030, USA.
SOURCE: CLINICAL CANCER RESEARCH, (1997 Dec) 3 (12 Pt 2) 2723-33. Ref: 101
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Biography
Historical
(LECTURES)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990303

AB The purpose of this study was to review the progress in clinical and translational research in chronic myelogenous leukemia (CML) over the past 20 years at M.D. Anderson ***Cancer*** Center. The CML database updating the clinical and basic research investigations was reviewed as the source of this report. Publications resulting from these investigations were summarized. The long-term results with intensive chemotherapy, IFN-alpha therapy alone or in combination, autologous stem cell transplantation, and new agents such as homoharringtonine and ***decitabine*** showed encouraging results. Biological studies related

to the BCR-ABL molecular abnormality, other molecular events, and the detection of minimal residual disease were detailed. Future strategies with potential promise in CML were outlined. Significant progress in understanding CML biology and in ***treating*** patients afflicted with the disease has occurred. Several therapeutic and research tools are currently investigated, which should hopefully improve further the prognosis of patients with CML.

L5 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:11948 CAPLUS
DOCUMENT NUMBER: 135:101701
TITLE: Decitabine (superGen)
AUTHOR(S): Manoharan, Arumugam
CORPORATE SOURCE: Department of Clinical Haematology St George Hospital, University of New South Wales, Sydney, Australia
SOURCE: IDrugs (2000), 3(12), 1525-1533
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. ***Decitabine*** , a potent DNA methyltransferase inhibitor, which was originally under development by Pharmachemie, is being developed by SuperGen. Pharmachemie had been studying ***decitabine*** in phase II clin. trials for several leukemia indications in Europe and the US. Preliminary results indicated that the compd. was active in the ***treatment*** of myelodysplasia, relapsed leukemia, acute myeloid leukemia and postallogeneic progenitor cell transplant relapse. The compd. is in phase II clin. trials with phase III trials scheduled to begin shortly. ***Decitabine*** has been used to ***treat*** myelodysplastic syndrome in a total of 125 patients, with an overall response rate of 49%. In a study using ***decitabine*** to ***treat*** chronic myelogenous leukemia in 81 patients, a response rate of 62% among patients in chronic phase of the disease was achieved. In a phase I/II trial designed to establish safety and efficacy in the ***treatment*** of sickle cell anemias ***treatment*** with ***decitabine*** generated a response in 100% of the patients tested: a total of eight patients were enrolled, each experienced elevated levels of fetal Hb. Side effects were minimal and the drug was well tolerated. Plans for addnl. clin. studies of ***decitabine*** as a ***treatment*** for sickle cell anemia are underway. A phase II trial using a low dose of ***decitabine*** in patients with myelodysplastic syndrome has been completed. Of 66 patients entered, 62 were evaluable. The response rate was 48%, with a median response duration of 40 wk. The mean survival from the start of therapy was 13 mo. In a study with 37 CML patients, a 25% overall response rate was seen in those patients in the blastic phase of the disease, and a 52% response rate was obsd. in the accelerated phase patients. The most significant side effect was prolonged myelosuppression. The drug suppresses cellular growth in seven human ***tumor*** cell lines, possibly by reactivation of certain growth suppressor genes.
REFERENCE COUNT: 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:268786 CAPLUS
DOCUMENT NUMBER: 132:288204
TITLE: DNA methylation inhibitors in the treatment of leukemias, myelodysplastic syndromes and hemoglobinopathies: clinical results and possible mechanisms of action
AUTHOR(S): Lubbert, M.
CORPORATE SOURCE: Department of Medicine, Division of Hematology/Oncology, University of Freiburg Medical Center, Freiburg, D-79106, Germany
SOURCE: Current Topics in Microbiology and Immunology (2000), 249(DNA Methylation and Cancer), 135-164
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. As recently reviewed, cytosine hypermethylation

of numerous genes important in orderly cell proliferation and maturation (many of them bone fide or p[redacted]tive ***tumor*** -suppresso[redacted]enes) is frequent in primary neoplasias and ***tumor*** cell lines. Therefore, the application of pharmacol. inhibitors of DNA methylation provides a conceptually attractive and rational approach to reverting these epigenetic changes in the ***malignant*** clone and re-establish the antiproliferative and possibly differentiation-inducing signals silenced by hypermethylation. 5-Azacytidine (azacitidine) and its deoxy congener 5-aza-2'-deoxycytidine (***decitabine***) have been clin. developed based on their strong in vitro and in vivo antileukemic activity at cytotoxic concns., and their differentiation-inducing potential at lower concns. in cell line models of hematopoietic and non-hematopoietic lineages. This paper reviews the mechanism of action, efficacy and safety of azacitidine and ***decitabine*** in ***treatment*** of acute myeloid leukemia, solid ***tumors*** , high-risk myelodysplastic syndrome, hemoglobinopathies and in .beta.-thalassemia in clin. studies.
REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:749198 CAPLUS
DOCUMENT NUMBER: 128:70449
TITLE: Results of decitabine therapy in the accelerated and blastic phases of chronic myelogenous leukemia
AUTHOR(S): Kantarjian, H. M.; O'brien, S. M.; Keating, M.; Beran, M.; Estey, E.; Giralt, S.; Kornblau, S.; Rios, M. B.; De Vos, D.; Talpaz, M.
CORPORATE SOURCE: Department of Hematology, MD Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Leukemia (1997), 11(10), 1617-1620
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of the study was to evaluate the activity of decitabine, a hypomethylating agent, in the treatment of patients with chronic myelogenous leukemia (CML) in transformation. Thirty-seven patients with CML in blastic (20 patients) or accelerated phases (17 patients) were treated. Their median age was 52 yr; 36 had Philadelphia chromosome-pos. disease. Decitabine was given at 100 mg/m2 over 6 h every 12 h .times. 10 doses (1000 mg/m2) to 13 patients, and at 75 mg/m2 over 6 h every 12 h .times. 10 doses (750 mg/m2) to 24 patients. In blastic phase, two patients (10%) achieved a complete hematol. response (one with Ph suppression), and three (15%) had a hematol. improvement (marrow CR, platelets <100 .times. 103/.mu.l), for an overall response rate of 25%. In accelerated phase, six patients (35%) returned to a second chronic phase (two with Ph suppression), one (6%) had a hematol. improvement, and two (12%) had a partial hematol. response, for an overall response rate of 53%. Prolonged myelosuppression was the most significant side-effect. The median time to recovery of granulocytes above 500/.mu.l was 48 days, and to recovery of platelets above 30 .times. 103/.mu.l, 31 days. Febrile episodes occurred in 25 patients (68%) including documented infections in 17 patients (46%). Decitabine has promising activity in CML. The most significant side-effect is prolonged myelosuppression. Decitabine may show activity in other myeloid disorders such as acute myeloid leukemia and myelodysplastic syndrome, as well as in other hematol. malignancies, alone or with other drug combinations. Its value in the context of stem cell support should also be investigated.

L5 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:261622 BIOSIS
DOCUMENT NUMBER: PREV200200261622
TITLE: Preclinical evaluation of the efficacy of STI571 in combination with a variety of novel anticancer agents.
AUTHOR(S): La Rosee, Paul (1); Johnson, Kara (1); Moseson, Erika M. (1); O'Dwyer, Michael (1); Druker, Brian J. (1)
CORPORATE SOURCE: (1) Division Hematology and Medical Oncology, Oregon Health and Science University, Portland, OR USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 839a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society

of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB STI571, a Bcr-Abl tyrosine kinase inhibitor has significant clinical activity in all phases of CML. Although durable responses have been seen in chronic phase patients, not all chronic phase patients achieve a cytogenetic response. Further, resistance or relapse during ***treatment*** with single agent STI571 have been observed in the majority of blast crisis patients. To determine whether the activity of STI571 could be enhanced, combinations of STI571 with other anti-leukemic agents were evaluated for activity against Bcr-Abl positive cell lines and in colony forming assays in vitro. We evaluated the cytotoxicity of arsenic trioxide (As2O3, Trisenox) and the chromatin modifiers 5-Aza-2-deoxycytidine (***decitabine***) and Trichostatin-A alone and in combination with STI571 against Bcr-Abl positive and negative cell lines and primary CML cells derived from chronic phase patients prior to ***treatment*** with STI571. As with other chemotherapeutic agents, significantly higher concentrations of As2O3 were required to achieve a 50% growth inhibition (IC50) of Bcr-Abl positive cell lines, K562 (1.11 muM+-0.075) and MO7p210 (1.99 muM+-0.22) than those required to inhibit the growth of Bcr-Abl negative cells, MO7e (0.81 muM+-0.18) and 32D (0.52 muM+-0.18). These levels of As2O3 are within a clinically achievable range. Cotreatment of K562 and MO7p210 cells with approximately equipotent doses of As2O3 and STI571 additively inhibits proliferation in a growth inhibition range up to 80%. Data analysis by the median-effect method (Chou & Talalay), which calculates the combination-index (CI) at different levels of inhibition, suggests that at >80% levels of inhibition, moderate synergy might be achievable. In colony forming assays using CML patient samples, combination ***treatment*** showed increased antiproliferative effects as compared with STI571 alone. Combinations of 0.1 or 0.25 muM STI571 with 0.4 or 0.8muM As2O3 (CFU-GM) and 0.8muM As2O3 (BFU-E) were significantly more potent in inhibiting colony formation as compared to ***treatment*** with STI571 alone. ***Decitabine*** is a hypomethylating agent that has activity in the ***treatment*** of CML blast crisis but has a narrow therapeutic window due to hematological toxicity. In MTT-assays with K562 cells, the combination of ***decitabine*** with STI571 revealed synergistic activity as seen by CI-values <1 at the IC50 (CI=0.6+-0.24) and IC75 (CI=0.6+-0.08) doses. This synergistic potential was also seen in MO7p210 cells (IC50: CI=0.81+-0.07 and IC75: CI=0.69+-0.1). Colony forming assays assessing the effects of ***decitabine*** on primary CML cells are ongoing. The triple combination of Trichostatin-A, a histone deacetylase inhibitor, ***decitabine*** and STI571 indicate antagonism (CI>1), which is in contrast to findings in non-leukemic ***malignant*** cell lines, where the combination of Trichostatin-A and ***decitabine*** led to enhanced apoptosis compared to single agent ***treatment*** . Experiments are ongoing with combination of Trichostatin-A and STI571 and Trichostatin-A with ***decitabine*** to determine which of these combinations accounts for this antagonism. These data suggest that combinations of STI571 with As2O3 or ***decitabine*** might be considered as therapeutic alternatives that could circumvent resistance to STI571, particularly in patients with advanced disease.

L5 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:220223 BIOSIS
DOCUMENT NUMBER: PREV200200220223
TITLE: Treatment of high-risk myelodysplastic syndrome with 5-aza-2'deoxycytidine (decitabine): Effects on allele-specific hypermethylation and expression of p15/INK4B.
AUTHOR(S): Luebbert, Michael (1); Nguyen, Carvell; Daskalakis, Michael (1); Guldberg, Per; Koehler, Gabriele; Nguyen, Tu; Wijermans, Pierre W.; Jones, Peter A.
CORPORATE SOURCE: (1) Div. Hemat./Oncol., University of Freiburg, Freiburg Germany
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 622a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001

ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Background: Hypermethylation and silencing of genes has been described in solid ***tumors*** , leukemia and MDS. ***Treatment*** of patients (pts) with high-risk myelodysplastic syndrome (MDS) with drugs which inhibit DNA methylation (azacytidine, ***decitabine***), given at doses allowing for outpatient management, results in hematologic responses in at least half the pts. Of 21 high-risk MDS pts ***treated*** with low-dose ***decitabine*** (DAC), reversal of p15/INK4B hypermethylation in mononuclear bone marrow cells (MNC) had been noted in responding pts (Daskalakis et al., Blood 92:715a, 1998). We then wished to address whether a reversal of hypermethylation reflects selective cell killing, vs. demethylation at individual p15 alleles, of clonal cells. It is also unclear whether demethylation of the p15 gene (encoding a negative regulator of G1/S progression of the cell cycle) in bone marrow cells results in changes of p15 protein expression during DAC ***treatment*** . Methods: Methylation of the p15 5' region was quantified by methylation-sensitive single-nucleotide primer extension assay (Ms-SNuPE). In bone marrow MNCs from selected MDS pts (hematologic response to DAC, reversal of initial hypermethylation as measured by MS-SNuPE), allele-specific p15 methylation was examined by sequencing of bisulfite- ***treated*** , PCR-amplified DNA, by resolving different epigenotypes on denaturing gradient gel electrophoresis (DGGE) of PCR products (Aggerholm et al., ***Cancer*** Res. 59:436-441, 1999), or both. p15 protein expression in myeloid precursors was determined on bone marrow biopsies before and during ***treatment*** by immunohistochemical staining. Results: The concordance between Ms-SNuPE vs. DGGE and sequencing of cloned alleles in detecting p15 hypermethylation was 86%. DGGE and sequencing (which both visualize individual epigenotypes) revealed a heterogenous pattern of variably methylated p15 alleles in 6/8 pts (5 of which had an abnormal karyotype) prior to ***treatment*** . After 1 course of DAC, hypermethylated alleles were still present in 5/8 pts, with a pattern compatible with partial demethylation at individual alleles. Persistence of abnormal metaphases was 100% in 4 pts and 33% in one pt. After 4-6 courses of DAC, emergence of unmethylated alleles was accompanied by cytogenetic normalization. p15 protein expression was absent in 4/8 pts with p15 hypermethylation prior to DAC, and was induced following initial ***treatment*** (median 1 course, range 1-3) during persistence of abnormal metaphases. Conclusions: Reversal of hypermethylation, generation of partly demethylated p15 alleles, and induction of p15 protein were observed in bone marrow cells from MDS pts after the first course of DAC ***treatment*** . At this early timepoint of ***treatment*** , complete persistence of an abnormal karyotype was noted in most cases, suggesting that demethylation occurred in clonal cells. Emergence of fully demethylated p15 alleles and reversion to normal karyotype with continued ***treatment*** are indicative of subsequent suppression of clonal cells.

L5 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:209957 BIOSIS
DOCUMENT NUMBER: PREV200200209957
TITLE: Minimal effective dose of the hypomethylating agent Decitabine in hematopoietic malignancies.
AUTHOR(S): Issa, Jean-Pierre (1); Garcia-Manero, Guillermo (1); Mannari, Rajan (1); Thomas, Deborah (1); Giles, Frank (1); Cortes, Jorge (1); Estey, Elihu (1); Kantarjian, Hagop (1)
CORPORATE SOURCE: (1) Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 594a-595a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB 5-aza-deoxycytidine (***Decitabine***) is a cytosine analogue characterized by modification at the 5 position of Cytosine. In vitro, ***Decitabine*** has dual effects on normal and neoplastic cells. At high doses, it appears to cause DNA synthesis arrest due to covalent linkage with DNA-Methyltransferases (Mtase), which results in cytotoxicity

and apoptosis. At low doses, however, minimal cytotoxicity is observed, and the ***treated*** cells exhibit marked reduction in M[redacted]e activity, reduced overall and gene-specific DNA methylation and reactivation of silenced genes, including ***tumor*** -suppressor genes. In order to maximize the hypomethylating effects of ***Decitabine*** , we have conducted a phase I trial of multiple low dose schedules in patients with relapsed/refractory myeloid malignancies. Initially, patients were ***treated*** at 5 mg/m2 IV over 1 hour daily for 10 days (a dose 30 fold lower than the reported MTD). The dose was then escalated to 10, 15 and 20 mg/m2 daily for 10 days. Finally, a group of patients received 15 mg/m2 daily for 15 days then 20 days. A total of 39 patients were enrolled on the study. 3 did not complete the first course (one due to sepsis and death on day 2 and two due to rapidly rising counts) and were excluded from analyses. The drug was well tolerated overall, with one death due to neutropenic sepsis, and 5 asymptomatic elevations in SGPT and/or Bilirubin (four grade 2, one grade 3). Responses were seen at all dose levels, but 15 mg/m2 appeared to induce the most responses, with no further benefit for increasing the dose or duration of administration. There were 7 complete remissions (CR 19.4%, 95% CI 7 to 34%) and 7 partial remissions in the 39 evaluable patients, for a response rate of 39% (95% CI 28 to 61%). Seven additional patients had significant reductions in peripheral and/or bone marrow blasts but did not recover normal hematopoiesis. Responses were seen in refractory/relapsed AML (10/30), MDS (3/4), and CML (2/2). In most patients who responded, there was a very gradual diminution of blasts over 2-4 weeks, and eventual recovery of normal hematopoiesis at 4-5 weeks, suggesting a non-cytotoxic mode of action for this regimen Response duration ranged from 2 months to 10+ months. DNA methylation studies are ongoing, but p15 demethylation could be observed 5 days after ***treatment*** in 2 patients who subsequently achieved remission. We conclude that low-dose ***Decitabine*** is an effective agent in myeloid malignancies that appears to induce remissions in part through demethylation rather than cytotoxicity. The recommended (minimal effective) dose of ***Decitabine*** for Phase II and combination studies in hematopoietic and solid neoplasms is 15 mg/mg2 IV over 1 hour daily for 10 days.

L5 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:186732 BIOSIS
DOCUMENT NUMBER: PREV200200186732
TITLE: 5-Aza-2'-deoxycytidine induces cell cycle arrest in human myeloma cell lines at the G1 phase via p21WAF1 and the G2/M phase via the p38 map kinase signal transduction pathway.
AUTHOR(S): Lavelle, Donald (1); DeSimone, Joseph; Hankewych, Maria; Kousnetzova, Tatiana; Chen, Yi-Hsiang
CORPORATE SOURCE: (1) Department of Medicine, Westside Division, University of Illinois at Chicago, VA Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 378a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB De novo DNA methylation of the p16INK4a ***tumor*** suppessor gene occurs frequently in patients with multiple myeloma and mediates silencing of p16INK4a expression in human myeloma cell lines. The ability of the DNA demethylating drug 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) to demethylate and reactivate expression of hypermethylated, silenced ***tumor*** suppressor genes makes it an attractive, rational candidate chemotherapeutic agent for myeloma and other malignancies. Chronic administration of low doses of this drug were sufficient to reduce the incidence of precancerous colonic polyps and lung ***tumors*** in two mouse model systems, and induced a clinical response in 49% of patients with myelodysplastic syndrome. To what extent the mechanism of action of this agent is due to reactivation of silenced ***tumor*** suppressor gene expression is unknown. We have determined the effect of DAC on the growth and cell cycle kinetics of human myeloma cell lines to 1) evaluate its potential in the ***treatment*** of this disease and 2) investigate its mechanism of action. Growth inhibition of four human myeloma cell lines (HS-Sultan, ARH-77, OPM-2, RPMI 8226) was observed at low doses of drug (IC50=2-4X10-3 M) and was not associated with induction

of apoptosis as determined by PARP cleavage assays. DAC-induced RB dephosphorylation was associated with increased expression of p21WAF1 rather than induction of p16INK4a in dose-response and kinetics experiments. Experiments performed in p53 mutant myeloma lines and a p53 null HCT 116 line indicated that DAC induced p21WAF1 expression through a p53-independent mechanism. Increased phosphorylation of p38 map kinase was also induced in a dose-dependent manner following DAC ***treatment***. No effects on phosphorylation of ERK 1/2 were observed. DAC induced an S phase block 24 hours following drug addition (10-6 and 10-7 M DAC). By 48 hours cell cycle arrest at both the G1 and G2/M phases was apparent. Experiments were performed to separately analyze the roles of p21WAF1 and the p38 map kinase pathway in mediating cell cycle arrest. Arrest at the G1 phase was inhibited in cells expressing antisense p21WAF1 following retroviral transduction with an antisense p21WAF1 construct. The G2/M arrest was inhibited by the p38 map kinase inhibitor SB203580 (10muM). No effect of the ERK1/2 inhibitor PD098059 (10muM) was observed. Neither SB203580 or PD098059 inhibited the growth of untreated cells and therefore did not directly interfere with incorporation of DAC by inhibition of cell growth. Arrest at the G1 and G2/M phases was therefore induced through two separate, independent pathways. The reactivation of p16INK4a expression was not required for initiation of cell cycle arrest. These results demonstrate that DAC effectively inhibited the growth of human myeloma cell lines at low, clinically achievable doses suggesting that this drug may be an effective anti-myeloma therapeutic agent.

L5 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:153049 BIOSIS
DOCUMENT NUMBER: PREV200200153049
TITLE: Treatment of accelerated phase of Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML AP) with imatinib mesylate (STI571.
AUTHOR(S): Kantarjian, Hagop M. (1); O'Brien, Susan (1); Cortes, Jorge (1); Faderl, Stefan (1); Giles, Francis (1); Thomas, Deborah (1); Garcia-Manero, Guillermo (1); Albitar, Maher; Rios, Mary Beth (1); Shan, Jenny (1); Issa, Jean-Pierre (1); Resta, Debra; Capdeville, Renaud; Keating, Michael J. (1); Freireich, Emil J. (1); Talpaz, Moshe
CORPORATE SOURCE: (1) Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 141a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB 237 adult patients (pts) with Ph+ CML AP were ***treated*** with imatinib mesylate 400-600 mg P.O. daily at our institution as part of 2 Novartis sponsored multi-institutional multinational studies: Novartis 109 the pivotal study (N=58) and Novartis 114 the expanded access study (N=179). 193 pts are evaluable with more than 3 months of follow-up. 156 pts had the classical CML AP criteria (***Cancer*** 61:1441, 1988); 33 pts were ***treated*** for blasts 10-14%, blasts+pros 20-29%, or spleen gtoreq10 cm bcm or 50% increase over 4 weeks (modified CML-AP criteria); 4 pts had second chronic phase. 26 received imatinib mesylate 400 mg/D, and 167 pts had imatinib mesylate 600 mg/D. Their median age was 50 years. Overall, 162 pts (84%) achieved CHR, 107 (55%) had a cytogenetic response (Ph<90%): major (Ph<35%) in 79 (41%); complete (Ph 0%) in 57 (30%). With a median follow up of 8.4 months, 167 patients (87%) are alive. The estimated 1.5-year survival rate was 75%, and remission duration rate 61%. Prognostic factors associated with lower major CG response rates (pgtoreq0.02) were: age gtoreq60 yrs, splenomegaly gtoreq10 cm bcm, longer duration of chronic phase >3 yrs, WBC >10X109/L, marrow blasts gtoreq15%, and STI dose 400 mg daily. Prognostic factors associated with worse survival (p<0.02) were: age gtoreq60 yrs, hemoglobin <10 g/dl marrow blasts gtoreq15%, cytogenetic clonal evolution and STI dose 400 mg daily and failure to achieve major CG response. Patients ***treated*** with 600 vs 400 mg had significantly better major (44% vs 19%, p=0.02) and complete (32% vs 15%, p=0.11) CG response rates, and 1.5 yr survival rates (78% vs 67%, p<0.01). Patients with "modified" CML AP criteria had similar major CG response and survival rates. By multivariate analysis, factors

independently predictive negatively for major CG response were (p<0.05): diagnosis to therapy >3 year and spleen size >10 cm bcm. The associated with worse survival were (p<0.05): older age, failure to achieve major cytogenetic response, and cytogenetic clonal evolution. In summary imatinib mesylate is the most active single agent therapy in accelerated phase. Imatinib mesylate combinations with interferon alpha, cytarabine, homoharringtonine, ***decitabine*** or others are warranted in CML AP.

L5 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129878 BIOSIS
DOCUMENT NUMBER: PREV200200129878
TITLE: Reactivation of a silenced, methylated p16INK4a gene by low-dose 5-aza-2'-deoxycytidine requires activation of the p38 map kinase signal transduction pathway.
AUTHOR(S): Lavelle, Donald (1); DeSimone, Joseph; Hankewych, Maria; Kousnetzova, Tatiana; Chen, Yi-Hsiang
CORPORATE SOURCE: (1) Department of Medicine, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 105a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB DNA methylation silences the expression of multiple ***tumor*** supressor genes in many types of ***tumors*** by inducing repressive chromatin structures mediated by binding of methylated DNA binding (MBD) proteins associated with protein complexes containing histone deacetylase (HDAC) activity and chromatin remodeling factors. ***Treatment*** with the DNA demethylating drug 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) reactivates the expression of silenced, methylated ***tumor*** suppressor genes by alleviating methylation-mediated repression. The synergistic reactivation of silenced, methylated genes by a combination of the HDAC inhibitor trichostatin A with low doses of DAC inducing limited demethylation demonstrated the important role of HDAC in the maintenance of methylation-mediated gene silencing (Cameron et al, Nat Genet 21:103, 1999). Whether DAC induces other activities that may be essential in the reactivation of silenced, methylated genes has not been investigated. Environmental and pharmacologic stress activates alternative map kinase signal tranduction pathways resulting in MSK 1-mediated phosphorylation of a minute fraction of histone H3 on serine 10. Phosphorylation of H3 increases sensitivity to hyperacetylation by HDAC inhibitors and histone acetyltransferases. Our objective in these experiments was to: 1) determine whether DAC ***treatment*** activated map kinase signal transduction pathways, and 2) investigate the role of map kinase pathways in the reactivation of silenced, methylated ***tumor*** suppressor genes. We observed that DAC ***treatment*** reactivated expression of a silenced, methylated p16INK4a gene in HS-Sultan cells in a dose-dependent manner (10-7 to 10-6 M). Phosphorylation of p38 map kinase was increased in a linear, dose-dependent manner at DAC concentrations ranging from 10-8 to 10-6 M. No activation of ERK 1/2 was observed. Increased phosphorylation of p38 was observed as early as 12 hours following drug addition. The ability of DAC to reactivate p16INK4a expression was inhibited by the p38 map kinase inhibitor SB203580 (10muM) at low doses (10-7 M) but not high doses (10-6 M) of DAC. The degree of inhibition was reduced with increasing DAC dose. The ERK 1/2 inhibitor PD098059 had no effect. Neither SB203580 or PD098059 affected cell growth and therefore the inhibition of p16INK4a reactivation was not due to inhibition of DAC incorporation into DNA H89 (10muM), at a concentration shown to preferentially inhibit MSK 1 (Thomson et al, EMBO J:4779, 1999), also inhibited reactivation of p16INK4a at low doses of DAC, suggesting that MSK 1-mediated histone H3 phosphorylation was required for p16INK4a reactivation. Our results demonstrate that activation of the p38 map kinase signal transduction pathway is required for reactivation of a silenced methylated p16INK4 gene by low dose DAC and suggest that this is due to the induction of an active chromatin configuration through phosphorylation of histone H3 by MSK 1. Therefore, reactivation of a silenced, methylated p16INK4a ***tumor*** suppressor gene at low doses of DAC requires both a reduction of DNA methylation density leading to

loss of repressive MBDHDAC complexes and induction of an active chromatin configuration through the p3[redacted]ap kinase signal transduction [redacted]hway.

L5 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129870 BIOSIS
DOCUMENT NUMBER: PREV200200129870
TITLE: Depsipeptide (FR901228) induces lysine-specific histone acetylation, differentiation and apoptosis in acute myeloid leukemia cells and demonstrates synergy with decitabine.
AUTHOR(S): Maghraby, Eman A. (1); Murphy, Thimoty (1); Parthun, Mark R.; Klisovic, Marko (1); Sklenar, Amy; Archer, Kellie J. (1); Whitman, Susan (1); Grever, Michael R. (1); Caligiuri, Michael A. (1); Byrd, John C. (1); Marcucci, Guido (1)
CORPORATE SOURCE: (1) Comprehensive Cancer Center, Ohio State University, Columbus, OH USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 103a-104a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Alterations in histone acetylation and, in turn, chromatin remodeling are important mechanisms in leukemogenesis. In t(8;21)(q22;q22) AML, the AML1/ETO fusion protein disrupts normal hematopoiesis by recruiting the transcription repressor histone deacetylase (HDAC) complex NCOR/Sin3/HDAC1 to AML1 target genes. The importance of histone acetylation to other types of AML is uncertain. We Studied the biological effects of depsipeptide (FR901228), a HDAC inhibitor currently in clinical trials, on both AML1/ETO-positive and negative AML cell lines and primary leukemia cells. Following 24-hour exposure of AML1/ETO-positive Kasumi-1 cell line to 0.1 to 100 nmol/L depsipeptide, increasing histone H3 and H4 acetylation levels were noted by immunoblotting analysis. These changes occurred in a specific pattern of lysine residue acetylation (i.e., more pronounced at H4 K5, 8 and 12 and less at K16). A significant depsipeptide-induced dose-dependent (0.1 to 100 nmol/L; $p<0.0001$) and time-dependent (4 to 96 h; $p<0.0001$) decrease in cell viability was found as assessed by trypan blue and annexin-V/PI staining. Similar findings relative to loss of viability and change in histone acetylation were observed in the K562 cell line and in primary leukemia cells. As histone deacetylase inhibitors have been shown to promote differentiation and enhance transcription, we examined for both processes concurrent with in vitro ***treatment*** in the Kasumi-1 cell line. Up-regulation of CD11b, a myeloid differentiation antigen, and expression of IL-3, an AML1 target gene, following exposure to depsipetide was demonstrated by flow-cytometry and RT-PCR assays, respectively. We next examined if agents that reverse methylation (ie. ***decitabine***) also increase histone acetylation and apoptosis in AML cells. These studies demonstrated that ***decitabine*** (2.5 umol/L) could enhance histone H4 acetylation at low levels of depsipeptide (1 nmol/L) ***treatment*** as compared to depsipeptide or ***decitabine*** alone. Enhanced acetylation of H4 was associated with a significantly higher 24-h apoptosis rate as compared to either agent alone. These data demonstrate that depsipeptide has significant ***antitumor*** activity in AML1/ETO-positive cells, and appears to promote transcriptional activation, differentiation, and apoptosis concurrent with increase in H3 and H4 histone acetylation. Furthermore, enhanced acetylation induced by ***decitabine*** markedly increases apoptosis. These results provide a rationale for trials with both single agent depsipeptide and those combining despipeptide with ***decitabine*** for AML ***treatment*** that target the pharmacodyamic endpoint of increasing histone acetylation in blast cells.

L5 ANSWER 18 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:320169 BIOSIS
DOCUMENT NUMBER: PREV200100320169
TITLE: Mechanism of induction of p21WAF1 by low dose decitabine in human myeloma cell lines.
AUTHOR(S): Lavelle, Donald (1); Chen, Yi-Hsiang; Hankewych, Maria; Kouznetsova, Tatiana; Patel, Kamini; DeSimone, Joseph
CORPORATE SOURCE: (1) Medicine, University of Illinois at Chicago, Chicago, IL USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 755a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Therapy with low-dose 5-aza-2'-deoxycytidine (decitabine; DAC), a DNA hypomethylating agent, is effective in the treatment of myelodysplastic syndrome and sickle cell disease. Because silencing of INK4 gene expression by DNA hypermethylation may be important in the development of multiple myeloma, the effect of DAC on cell growth, RB phosphorylation state, and expression of p16INK4a and p21WAF1 have been investigated in four human myeloma cell lines (ARH-77, OPM-2, RPMI 8226, HS-Sultan) to determine its potential in the treatment of multiple myeloma and to investigate its mechanism of action. Growth inhibition of all lines was observed at doses (IC50 = 2-4 X 108 M) not associated with significant apoptosis (<5% PARP cleavage). Hypermethylation of the INK4a gene correlated with lack of p16 protein expression. Demethylation of the INK4a gene was detected 48 hours after addition of DAC (10-6M) correlating with the onset of p16 protein expression. Expression of p16 protein was dose-dependent between 10-6 and 10-7 M DAC but was not detected at 10-8 M. RB dephosphorylation was observed 24 hours following DAC addition, preceding the appearance of p16, and occurred even at the 10-8 M dose. The expression of p21WAF1 increased in a similar time and dose-dependent manner as RB dephosphorylation. DAC increased the level of p21WAF1 protein 3-4 fold and the transcriptional activity of a p21 promoter-luciferase construct 4-5 fold at the 10-8 M dose. Stability of the p21 mRNA and protein was unchanged, indicating that transcriptional induction of the p21 promoter was responsible for the p21WAF1 increase. Inhibition of DNA methyltransferase (DNMT) expression by antisense oligonucleotides also increases p21WAF1 transcription (J Biol Chem 275:6353, 2000) and therefore it is likely that the activity of DAC is due to inhibition of DNMT. In contrast to the lack of apoptosis observed following DAC treatment (<5% PARP cleavage), extensive apoptosis accompanied treatment with hydroxyurea (40% PARP cleavage). Because low doses of DAC increase p21WAF1 and induce RB dephosphorylation with minimal apoptosis, its mechanism of action as a low-dose therapeutic agent in the treatment of myelodysplastic syndrome may involve induction of differentiation rather than cytotoxicity. The use of DAC as a therapeutic agent in the treatment of multiple myeloma deserves further investigation.

L5 ANSWER 19 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:305332 BIOSIS
DOCUMENT NUMBER: PREV200100305332
TITLE: TroxatylTM (Troxacitabine) has activity in blastic phase chronic myeloid leukemia (CMLBP.
AUTHOR(S): Giles, F. J. (1); Cortes, J. E. (1); Bivins, C. (1); Andreeff, M. (1); Talpaz, M. (1); Jolivet, J.; Kantarjian, H. M. (1)
CORPORATE SOURCE: (1) Departments of Leukemia, Bioimmunotherapy, and Bone Marrow Transplant, UT MD Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 254b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB TroxatylTM is the first dioxolane nucleoside with potent in vitro and in vivo ***antitumor*** activity. This cytosine analog is a DNA polymerase inhibitor and complete DNA chain terminator. It undergoes cellular uptake with prolonged retention of the phosphorylated metabolites, TroxatylTM is not a substrate for cytidine deaminase and is the only L-isomer nucleoside analog with anti- ***tumor*** activity. In a Phase I study of TroxatylTM in patients (pts) with primary refractory or relapsed acute leukemia, mucositis and hand-foot syndrome were the dose

limiting toxicities. (Giles et al Abstract 4231 ASH 1999). The recommended single agent dose was defined as 8 mg/m2/day daily for 5 days. Preliminary results are presented for 13 pts (10 female and 3 male, median age: 52 years; range:23-80), with CMLBP ***treated*** at this dose as part of an ongoing Phase II study. Prior therapy for CML chronic phase included hydroxyurea alone (1 pt), alpha interferon-based therapy (7 pts), homoharringtonine (HHT) (1 pt), allogeneic Stem Cell Transplantation (SCT) (1pt). Eleven pts had received and failed one or more prior therapy for CMLBP including topotecan-based therapy (5 pts), allogeneic SCT (3 pts), 6-thioguanine (1 pt), HHT (2 pts), mitoxantrone/ara-C (1 pt), STI (5 pts), donor lymphocyte infusions (1 pt), 2-CDA/cyclophosphamide/VP16 (1 pt), hCVXD (1 pt), clofarabine/ ***decitabine*** (1 pt), liposomal Daunorubicin/ara-C (1 pt), CVAD (1 pt). Toxicities included: Grade 2 skin rash - 5 pts; hand-foot syndrome: Grade 2-4 pts, Grade 3 - 3 pts; Grade 2 mucositis - 1 pt; Grade 4 mucositis - 2 pts. Three patients were converted to 2nd chronic phase with a median duration of 10 months (range 9-16). Two pts had early deaths from progressive disease and two others are too early to assess. Four patients have received two or more courses of therapy. TroxatylTM has activity in heavily pretreated patients with CMLBP and merits further study in first line as a single agent and in combination.

L5 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:301438 BIOSIS
DOCUMENT NUMBER: PREV200100301438
TITLE: Decitabine and sodium butyrate reactivate expression of a silenced Stat-1 and enhance interferon-responsiveness in the HS-Sultan cell line.
AUTHOR(S): Lavelle, Donald (1); Chen, Yi-Hsiang (1); Hankewych, Maria (1); Kourznetsova, Tatiana (1); DeSimone, Joseph (1)
CORPORATE SOURCE: (1) Medicine, Westside Division, VA Chicago, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 302a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Silencing of Stat-1 gene expression may mediate changes in the growth, survival, and response to interferon of ***cancer*** cells. The level of expression of Stat-1, Stat-2, Stat-3, and Stat-5 in five human myeloma cell lines (ARH-77, HS-Sultan, OPM-2, RPMI 8226, U266) was measured to assess whether alterations of Stat gene expression are associated with multiple myeloma. Constitutive expression of these genes was observed by Western blot analysis in all lines except HS-Sultan, in which the expression of Stat-1 was nearly undetectable. ***Treatment*** of HS-Sultan cells with the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) and the histone deacetylase inhibitors, sodium butyrate and trichostatin A, reactivated Stat-1 mRNA and protein expression as observed by Northern and Western blot analysis. The addition of interferon-alpha resulted in phosphorylation of the Stat-1 protein in HS-Sultan cells pretreated with either ***decitabine*** or sodium butyrate. These results suggest that expression of the Stat-1 gene was silenced by DNA hypermethylation in the HS-Sultan line. The effect of reactivation of Stat-1 expression on the ability of interferon-alpha to inhibit cell growth was determined by measuring the effect of varying doses of interferon on the growth of untreated control cells compared to cells surviving a 72 hour pretreatment with either butyrate (1mM) or ***decitabine*** (1 X 10-6M). The percent growth inhibition by interferon-alpha (5000, 1250, 310 U/ml) of control cells was 52.1+-7.0, 43.3+-11.5 and 34.6+-10.9 (n=3), of ***decitabine*** -pretreated cells was 83.2+-6.5, 73.4+-10.1, and 66.0+-17.3 (n=3), and of butyrate-pretreated cells was 79, 65, and 63 (n=1) at the respective doses of interferon. Pretreatment of HS-Sultan with ***decitabine*** or butyrate, which results in reactivation of Stat-1 expression, thus also increases the response to interferon-alpha.

L5 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:261842 BIOSIS
DOCUMENT NUMBER: PREV199799568445

TITLE: Decitabine (5-Aza-2'-deoxycytidine; DAC) plus daunorubicin as a first line treatment in patients with acute myeloid leukemia: Preliminary observation.

AUTHOR(S): Schwartsmann, G. (1); Fernandes, M. S.; Schaan, M. D.; Moschen, M.; Gerhardt, L. M.; Di Leone, L.; Loitzembauer, B.; Kalakun, L.

CORPORATE SOURCE: (1) Hosp. Clin. Porto Alegre, Serv. Oncol., Rua Ramiro Barcelos, 2350/3 andar Leste, Porto Alegre, RS Brazil

SOURCE: Leukemia (Basingstoke), (1997) Vol. 11, No. SUPPL. 1, pp. S28-S31.
ISSN: 0887-6924.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The authors report on the preliminary results of an ongoing phase II trial whereby the combination of the new DNA hypomethylating agent, 5-Aza-deoxycytidine (DAC), plus daunorubicin was given as first-line induction therapy to non-pretreated patients with acute myeloid leukemia (except FAB M3). DAC was given as a 4-h intravenous infusion at the dose of 90 mg/m-2 daily from days 1-5, while daunorubicin was administered at the dose of 50 mg/m-2 on days 1-3. A maximum of two courses were given to the patients with an interval of 4-6 weeks. Up to now, eight patients were accrued, of those six were evaluable for toxicity and response. The main toxic effects were bone marrow suppression, mucositis, nausea and vomiting, and alopecia. All six patients achieved a complete remission after one (five cases) or two (one case) courses. The trial is open for patient accrual.

L5 ANSWER 22 OF 23 EMBASE

ACCESSION NUMBER: 1998096144 EMBASE

TITLE: Chronic myelogenous leukemia - Progress at the M. D. Anderson Cancer Center over the past two decades and future directions: First Emil J Freireich Award Lecture.

AUTHOR: Kantarjian H.M.; Talpaz M.; O'Brien S.; Kurzrock R.; Gutterman J.; Keating M.J.; McCredie K.B.; Freireich E.J.

CORPORATE SOURCE: H.M. Kantarjian, Department of Hematology, Box 61, 1515 Holcombe Boulevard, Houston, TX 77030, United States

SOURCE: Clinical Cancer Research, (1997) 3/12 II (2723-2733).
Refs: 101
ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The purpose of this study was to review the progress in clinical and translational research in chronic myelogenous leukemia (CML) over the past 20 years at M.D. Anderson ***Cancer*** Center. The CML database updating the clinical and basic research investigations was reviewed as the source of this report. Publications resulting from these investigations were summarized. The long- term results with intensive chemotherapy, IFN-.alpha. therapy alone or in combination, autologous stem cell transplantation, and new agents such as homoharringtonine and ***decitabine*** showed encouraging results. Biological studies related to the BCR-ABL molecular abnormality, other molecular events, and the detection of minimal residual disease were detailed. Future strategies with potential promise in CML were outlined. Significant progress in understanding CML biology and in ***treating*** patients afflicted with the disease has occurred. Several therapeutic and research tools are currently investigated, which should hopefully improve further the prognosis of patients with CML.

L5 ANSWER 23 OF 23 SCISEARCH

ACCESSION NUMBER: 1998:653467 SCISEARCH

THE GENUINE ARTICLE: ZZ632

TITLE: Interesting responses in patients with advanced nonsmall lung ***cancer*** after ***treatment*** with the DNA-methylation inhibitor, 5-aza-2'-deoxycytidine (***decitabine***)

AUTHOR: Momparler R L (Reprint); Ayoub J; Dionne J; Belanger K

CORPORATE SOURCE: HOP NOTRE DAME DE BON SECOURS, CTR ONCOL, MONTREAL, PQ H3T 1C5, CANADA, HOP ST JUSTINE, CTR RECH PEDIAT, MONTREAL, PQ H3T 1C5, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: ANNALS OF ONCOLOGY, (SEP 1998) Vol. 9, Supp. [2], pp. 630-630.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0923-7534.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

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